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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/403,539	10/22/1999	NICHOLAS M. DEAN	ISIS-3013	7420
32650	7590	06/30/2004	EXAMINER	
WOODCOCK WASHBURN LLP ONE LIBERTY PLACE - 46TH FLOOR PHILADELPHIA, PA 19103			ZARA, JANE J	
			ART UNIT	PAPER NUMBER
			1635	

DATE MAILED: 06/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/403,539

Applicant(s)

DEAN ET AL.

Examiner

Jane Zara

Art Unit

1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 April 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 37-42 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 37-42 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 9-03.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 4-5-04.

Claims 37-42 are pending in the instant application.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Claims 37, 38, 40 and 41 are rejected under 35 U.S.C. 102 (e) as being anticipated by Muller et al for the reasons of record set forth in the Office action mailed 1-6-04.

Applicant's arguments filed 4-5-04 have been fully considered but they are not persuasive. Applicants argue that the Muller patent presents many options for compositions that show increased stability and hybridize to PKC and that one would have to pick and choose from the many variables presented in the Muller patent, which is plainly inconsistent with a finding of anticipation. Contrary to Applicants' assertions, the Muller patent teaches the incorporation of at least one methylene methylimino (MMI) modified internucleotide linkage into an oligonucleotide (and which oligonucleotide also comprises at least one phosphodiester internucleotide linkage) for enhancing oligonucleotide stability. Muller teaches the oral administration of oligonucleotides with enhanced stabilizing structures, including the previously taught stabilizing structure, MMI, in combination with at least one phosphodiester internucleotide linkage. Claims

37, 38, 40 and 41 of the instant invention are drawn to a method of administering to the alimentary canal of a mammal (e.g. including oral administration) an oligonucleotide comprising at least one MMI and at least one phosphodiester linkage. The generically described oligonucleotides comprising at least one MMI and one phosphodiester internucleotide linkage are therefore anticipated by the teachings of Muller, and the instant 102 rejection is maintained.

Claims 37-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Muller et al in view of Agrawal et al for the reasons of record set forth in the Office action mailed 1-6-04.

Applicants argue that there is no motivation to combine the references of Agrawal and Muller to render the instant invention obvious, and that no motivation exists to pick and choose and arrive at the claimed invention. Contrary to Applicants' assertions, Muller teaches the incorporation of at least one MMI linkage for enhancing the stability of oligonucleotides. Muller teaches the oral administration of oligonucleotides. And Agrawal teaches the increased oral availability of oligonucleotides with modified internucleotide linkages. Since MMI internucleotide linkages were well known in the art to enhance oligonucleotide stability, and oral administration was well known in the art to lead to degradation of oligonucleotides, one of ordinary skill would have been motivated to incorporate MMI linkages into oligonucleotides in combination with phosphodiester linkages for oral administration. Applicants argue that nothing in the cited art teaches alternating MMI and phosphodiester internucleoside linkages. Since the incorporation of MMI linkages in

various configurations would be expected to enhance the stability of (including the oral bioavailability of) oligonucleotides compared to oligonucleotides comprising phosphodiester linkages alone, and since the instant disclosure does not teach any unexpected results, and in fact does not teach any comparison in the bioavailability of oligonucleotides comprising an alternating configuration (of MMI linkages and unmodified oligonucleotides) following oral administration, the claimed configuration is a design choice and is therefore obvious.

No comparisons have been provided for the oral bioavailability of the configuration claimed (i.e. alternating MMI and phosphodiester bonds) compared to unmodified and minimally modified (i.e. not alternating) oligonucleotides. No comparisons have been provided for the configurations shown in the specification (i.e. figure 3), which comprise blocks of MMI linkages (i.e. ISIS 14182, ISIS 14183 and unmodified ISIS 4189) that render these configurations free of the prior art. Absent evidence to the contrary, one of ordinary skill in the art would expect that the incorporation of MMI linkages in any configuration would enhance the stability of oligonucleotides in a hostile environment (the alimentary canal) compared to unmodified oligonucleotides (i.e. with only phosphodiester bonds). Therefore the instant claims stand rejected as being obvious in light of the prior teachings of Muller and Agrawal.

Conclusion

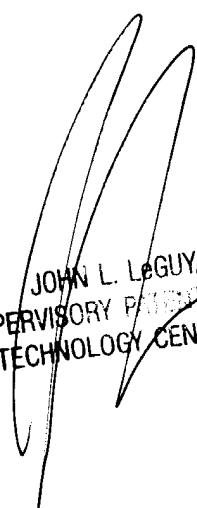
THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is **703-872-9306**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. **NO DUPLICATE COPIES SHOULD BE SUBMITTED** so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765**. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (571) 272-0760. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JZ
6-20-04



JOHN L. LEGUYADER
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600